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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,184	04/07/2004	Bruce S. Kristal	10845-148	7390

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/820,184	KRISTAL ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *1-29 and 42-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-41* is/are rejected.

7)☒ Claim(s) *31 and 36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/25/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions Acknowledged

1. Acknowledgment is made of applicant's election, without traverse, with Group II invention along with promethazine and stroke as the elected species. Claims 30-41 read on the elected species. Claims 1-29 and 42-45 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Objections

2. Claims 31 and 36 are objected to because of the following informalities: Misspelling of "amoxepine" is present. Applicant is suggested to amend "amoxepine" to "amoxapine".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims are rejected under 35 USC 112, first paragraph, because the specification while being enabling for treating the specific mitochondrial component mediated disease (e.g., stroke, and heart attack) with the administration of the specific compound that inhibits mitochondrial permeability transition (e.g., methiothepin, promethazine, triflupromazine, clomipramine, flufenzaine, chlroprothixene, etc...), does not reasonably provide enablement for "protecting or treating a subject against a mitochondrial component-mediated disease" with the administration of "a compound effective in inhibiting mitochondrial permeability transition". The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the nature of the invention; the state of the prior art; the relative skill of those in the art; the predictability or unpredictability of the art; the breadth of the claims; the amount of direction or guidance presented; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant claims are drawn to a method for "protecting a subject against a mitochondrial component mediated disease comprising administering...an effective amount of a compound effective in inhibiting mitochondrial permeability transition" (claims 30-34) and "treating a subject against a mitochondrial component mediated disease comprising administering...an effective amount of a compound effective in inhibiting mitochondrial permeability transition" (claims 35-41).

The Webster's II Dictionary (New Riverside University Dictionary, 1984) defines the term "protect" as "to keep from harm, attack, or injury ". The interpretation of the instant claims (given "broadest reasonable interpretation") allows for inclusion of preventing or curing effects of said mitochondrial component mediated disease conditions by the administration of said compounds.

The claims are very broad due to the vast number of possible compounds of that are described as being "a compound" that inhibits mitochondrial permeability transition. The instant claims cover mitochondrial permeability transition inhibiting compounds that are known to exist and those that may be discovered in the future. Also, the breadth of scope of the invention is further exacerbated by plethora of diseases encompassed by the instant claims, for example various neurodegenerative diseases stroke, myocardial infarction, reperfusion injury to organs, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, diabetes, senile dementia, dysplasia, myelitis, spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, Refsum's disease, abetalipoprotemia, ataxia, telangiectasia, mitochondrial multi.system disorder, transverse myelitis, anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy, Down's Syndrome in middle age, Diffuse Lewy body disease, Wernicke-Korsakoff syndrome, chronic alcoholism; Creutzfeldt-Jakob disease, Subacute sclerosing panencephalitis, Hallerrorden-Spatz disease, Dementia pugilistica, etc..., that are known today, and those that may be discovered in the future.

With respect to the scope of enablement for "protecting a subject affected with a mitochondrial component mediated disease",

It is generally known today that there is no cure of Alzheimer's disease, Parkinson's disease, multiple scleroris, stroke and heart attack. The true fact of the state of the art is illustrated succinctly in the "Alzheimer's: Searching for a Cure", Linda Bren, www.fda.gov, 2003; "NIH Heart Disease & Stroke Research: Fact Sheet" (American Heart Association, 2004);

"Cardiovascular Disease: Treatment for Stroke", Stanford Hospital & Clinics, 2003; "Alzheimer's disease: Treatment Overview", WebMD, 2005; "Acute Congestive Heart Failure", Thomas N. Levin, Postgraduate Medicine, Vol. 101, No. 1, 1997).

Furthermore, it is known today that progress in treating Parkinson's disease or Alzheimer's disease is hampered by the lack of good animal models, lack of validated targets, barriers in the design and implementation of clinical trials and/or lack of surrogate markers ("Alzheimer's Disease", Saloni Tanna, 2004; "Parkinson's Disease and FGF Receptor in Gene Therapy", Stachowiak et al., www.parkinsonalliance.org., 2000). Thus, it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the protective, preventive or completely curing or eradicating effect.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmacy art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the preventive utility of the instant compounds.

The specification provides the effects of promethazine in reducing 3-nitropropionic induced lesions or MPTP induced cell damage in vivo (rat study) and the effects of nortriptylene in reducing in infarct size and OGD-mediated caspase-3 activation and cytochrome C release (Examples 1 and 2). However, there is no demonstrated correlation that the tests and results apply to the claimed protective utility embraced by the instant claims.

Since the efficacy of the claimed compound(s) in protecting a mitochondrial component mediated diseases mentioned above, for example Alzheimer's disease, Parkinsons's disease, multiple scleroris, stroke and heart attack cannot be predicted from a priori but must be

determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

With respect to scope of enablement for "a mitochondrial component mediated diseases" or "a compound effective in inhibiting mitochondrial permeability transition",

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5(BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 9999 F.2d 1577, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or

pharmaceutical activity of protecting or treating "mitochondrial component mediated disease" prior to filling of the instant invention was an unpredictable art.

To practice the instant invention to the claimed scope, applicant would have to (i) make or synthesize numerous possible compounds characterized as "a compound...inhibiting mitochondrial permeability transition" considering the structure-activity relationship of the compounds, (ii) screen potentially suitable compounds and (iii) extrapolate the test and result to the claimed therapeutic utility. In other words, the instant invention necessitates for the skilled artisan to undergo an exhaustive search for the embodiments suitable to practice the claimed invention.

Where the physiological activity of a chemical or biological compound is considered to be an unpredictable art (Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)), the skilled artisan would have not known how to extrapolate the result provided in the instant specification to the larger and highly varied genera of compounds that are characterized by "a compound...inhibiting mitochondrial permeability transition" , without undue amount of experimentation.

Although the specification discloses certain tricyclic or phenothiazine compounds such as "methiothepin, promethazine, triflupromazine, clomiprmaine, flufenzaine, chlorprothixene, nortriptyline, promazine...." as the suitable "a compound...inhibiting mitochondrial permeability transition", the specification fails to provide how to make/screen numerous "a compound...inhibiting mitochondrial permeability transition" without undue amount of

experimentation. As discussed in preceding comments, in the instant case, only a limited number of compounds that are structurally or functionally similar to promethazine or nortriptyline which are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The instant claims read on any compounds having "a compound...inhibiting mitochondrial permeability transition ", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

As discussed above, considering above factors, especially the "sufficient working examples", "the level of skill in the art", "the relative skill and the unpredictability in the pharmaceutical art", "breadth of the claims" and "the chemical nature of the invention", one having ordinary skill in the art would have to undergo an undue amount of experimentation to practice the invention commensurate in scope with these claims.

The examiner acknowledges that the Office does not require the present of (all) working examples to be present in the disclosure of the invention (see MPEP 2164.02). However, given the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to make and use the full scope of the presently claimed invention without undue amount of experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is a reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently claimed subject matter. Absent such evidence or

reasoning, applicant has failed to obviate the rejection of the instant claims under 35 USC 112, first paragraph (for the lack of scope of enablement).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 34 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34 and 39 recites "said disease is stroke, heart attack, neurological insult, brain trauma, spinal cord injury, chemical toxicity, liver, muscle, kidney reperfusion or a combination thereof". It is not clear what "liver, muscle" refers to. Does it refer to liver reperfusion or muscle reperfusion? Particularly, missing operator "or" before kidney leaves the reader in doubt as to the meaning of "liver, muscle, kidney reperfusion" to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 30-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Olney (US 4833138).

Only teaches a use of phenothazinealkaneamine compounds presented by the formula I including 10-[2-(dimethylamino)propyl]phenothiazine (commonly known as promethazine) or its salt for the treatment of brain damage or neurodegenerative disease associated with anoxia or ischemia such as stroke, cardiac arrest or perinatal asphyxia (abstract; column 1, lines 6-12; column 3, lines 17-23; column 4, line 64; claim 6), wherein said compound is administered in dosage range of from about 0.1mg to about 10 mg per kilogram of body weight (column 10, lines 11-19).

With respect to the activity of said compound in "inhibiting mitochondrial permeability transition", such functional characteristic or property deems to be inherent to the referenced method. The prior art directing the administration of same compound, in overlapping dosage amount, inherently possessing therapeutic effects for the same ultimate purpose as disclosed by the applicant anticipates the applicant's invention even absent explicit recitation of underlying mechanism.

Conclusion

6. No Claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
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